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NOVARTIS

March 23, 1999

Dockets Management Branch
HFA-305
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98D-1266: Draft Guidance for Industry on Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling

Dear Sir or Madam:

Novartis Pharmaceuticals Corporation ("Novartis") is pleased to provide comments on the recently released Draft Guidance to Industry. Novartis is concerned that the procedures described in the guidance will not significantly "contribute to the accurate and safe selection of drug products by health care practitioners", and could, in fact, result in additional confusion and potential harm to patients.

Dubious Public Health Benefit

In the "Background" section, the guidance document states that "(w)hen multiple reference listed products exist with the same established names and strengths, chances increase that a generic product will be dispensed to a patient that is not therapeutically equivalent to the one intended or previously prescribed." Does FDA have data suggesting this has happened, or by how much the chances of dispensing error increase with the introduction of multiple generic products? If so, these data should be made available in the docket for public review and comment. Such evidence would enhance any potential beneficial impact of this guidance, especially for those products with multiple reference listings.

The draft guidance also states that "inclusion of a therapeutic equivalence code on prescription drug labels/labeling is voluntary" and that only "in certain cases where safety issues are raised the Agency may ask that a...code be included." Therefore, the likely result of this approach is that only those products that FDA has deemed to be therapeutically equivalent to an innovator product will be identified. There is no "fair balance" requirement for "B"-coded products to be similarly identified, so the uncertainty surrounding selection of therapeutically equivalent products by health care practitioners will remain. It is extremely unlikely, for example, that *any* of the four inequivalent reference listed diltiazem extended-release capsules cited in the Guidance document would be labeled by their manufacturers as being "BX" to the innovator product. Many generic companies may take advantage of the resulting confusion. Although the Agency states that brand name companies could indicate the "BX" status on their own product labels, it is unlikely that this would be sufficient. In fact, even a "B" code appearing on a product label could be erroneously interpreted as implying substitutability.

The preface of the *Orange Book* itself acknowledges that "(c)ertain drugs present special situations that deserve a more complete explanation than can be provided by the two-letter codes." The appearance of a therapeutic equivalence code on the product label in the absence of additional explanatory information can lead to confusion if a safety issue is identified, such as inappropriate product substitution, failure to meet potency standards or violations by the generic manufacturer of GMP regulations. Presumably, the Agency would take prompt corrective action in such a case, beyond merely requesting an alteration in the therapeutic equivalence code appearing on the label. However, such conceivable actions as a product recall could create additional confusion and have a profound detrimental impact on the brand name product that has been, in practical effect, "linked" with the product in question.

Additional confusion could arise in those instances when the proper use of a product requires the use of an associated monitoring system to minimize the risk of adverse events. Such systems are designed and administered in cooperation with the product manufacturer for patients who receive the innovator product. The appearance of a therapeutic equivalence code on a generic product's label may give rise to the notion that the related monitoring systems are also equivalent and deemed by FDA to be interchangeable.

Since most prescriptions are repackaged by the pharmacist prior to being dispensed (with the exception of "unit of use" packages – see below), the public is unlikely to see the equivalence code appearing on the product labeling, and practitioners will still be required to consult the *Orange Book* when questions arise concerning the substitutability of a given product. This is something they already do. Contrary to the Agency's assertion that the codes would increase utilization of the *Orange Book*, the converse is a more likely outcome, as pharmacists and other healthcare practitioners come to rely upon the code appearing on the product label as a "shorthand" indication of therapeutic equivalence.

Need for Full Disclosure

The guidance document contains no requirement for a definition of therapeutic equivalence or of the coding system. Patients who may be dispensed products in "unit of use" containers displaying a therapeutic equivalence code (and required acknowledgment of the innovator trademark and its holder) will have no understanding of what the code implies, for example, that:

- only the *innovator* product has been shown to be "safe and effective"
- the generic product has only been shown to meet an *in vitro* dissolution standard, or if tested *in vivo*, the tests are conducted only in healthy, adult volunteers, and not necessarily in patients with the disease
- differences exist in statistical methodology used to determine "bioequivalence", such as single-dose vs. multiple-dose and individual vs. population bioequivalence measures
- differences exist between "bioavailability" and "bioequivalence"

Furthermore, if these patients experience an adverse event while taking a generic product, additional problems could arise during resultant MedWatch reports or patient lawsuits. Since brand names are often easier to pronounce than generic names, a patient may inaccurately identify the innovator product when reporting the adverse event to his/her physician, who may be unaware that a substitution had occurred at the pharmacy.

FDA asserts its assumption that products "classified as therapeutically equivalent can be substituted with the full expectation that the substituted product as labeled will produce the same clinical effect and safety profile as the prescribed product." Even if true, there is no evidence that products deemed equivalent to a particular reference product are equivalent to *each other*. Absent a clear explanation of this, it is conceivable that inappropriate product substitutions will be made on the assumption that "if *A* is equivalent to C, and *B* is equivalent to C, therefore *A* must be equivalent to *B*".

Inconsistencies and Inaccuracies

The guidance document cites the 1984 Drug Price Competition and Patent Term Restoration Act (the 1984 Amendments) as the source of FDA's authority to "approve generic versions of approved drug products that have been shown through the ANDA process to be the same as the pioneer product." The same paragraph lists the Agency's interpretation of additional requirements for an ANDA, including that "the labeling for the proposed drug product is the same as that for the pioneer product." Both of these assertions are inaccurate. Generic products are not the "same" as a pioneer product, but rather, pharmacologically equivalent. Many aspects of generics differ from the previously approved innovator, and product labels differ on many points. However, patients could still be easily misled into believing that they are receiving "the same thing as" the innovator product, especially since a generic product label will now contain the trademark of a completely unrelated company's product.

In defining "therapeutic equivalence", and describing the criteria that must be met, further confusion arises. As mentioned earlier, generic products are only *assumed* by FDA to be safe and effective in patients if they meet the Agency's criteria for "pharmaceutical equivalence." There is no requirement for generic manufacturers to test the safety and effectiveness of their products. This is disturbing, because the criteria for "pharmaceutical equivalence" are apparently circumstantial, and compendial standards are often changed to meet generic needs. Many products have been deemed therapeutically equivalent without meeting the criterion that they "contain identical amounts of the same ingredient in the same dosage form" (e.g. nifedipine extended release products).

Another section of the guidance document refers to the repeal of section 301(l) of the Federal Food, Drug and Cosmetic Act ("FD&C Act") as the basis for FDA's determination that "it is legally permissible" to permit the placement of therapeutic equivalence codes on product labeling. This too, is an incorrect interpretation. That provision only concerned "representation(s) or suggestion(s) of approval". As the guidance document itself states, a therapeutic equivalence code signifies much more than mere approval, and is in fact a representation of FDA's determination that a "product may be safely substituted for another." Therefore, the repeal of section 301(l) is insufficient grounds for authorizing the procedures described in the guidance.

Finally, the Agency states it has received a number of requests from generic manufacturers to place therapeutic ratings on the label of the product and considers this to be "in the best interest of the public health." It is unlikely, however, that generic companies have asked for this labeling for any reason other than to facilitate generic substitution of their product for the innovator. Generic drug manufacturers will no longer need to purchase ads saying "Compare to _____" or "AB rated to _____", when that information can be provided on the product label. This amounts to little more than an advertising windfall for these manufacturers, with questionable public health benefit. There is no provision in the 1984 Amendments permitting ANDA applicants to capitalize on the innovator's trademark, as well as the innovator's reputation and goodwill in the health care professional and patient communities, to market its generic product.

Thank you for the opportunity to comment on this draft guidance.

Sincerely,

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Vice President, Global Drug Regulatory Affairs

cc: R. Bantham, PhRMA